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Original Article

ORIGINAL ARTICLE

Increased incidence and improved prognosis of glomerulonephritis: a national 30-year study

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ABSTRACT

Background. While there are many cross-sectional studies of glomerulonephritis (GN) incidence, changes in incidence over time, particularly in the 21st century have received less attention. Similarly, little is known about temporal changes in GN prognosis. The presence in Denmark of comprehensive registries for renal biopsy results, end-stage renal disease (ESRD), comorbidity and mortality permit these questions to be addressed.

Methods. Data for all renal biopsies in Denmark between 1985 and 2014 were extracted from the Danish Renal Biopsy Registry and Patobank registries. The date of first dialysis or transplantation was extracted from the Danish Nephrology Registry for those patients developing ESRD. Dates of death and presence of chronic comorbid conditions at date of biopsy were extracted from the National Patient Registry. The incidence of GN, adjusted to the 2013 European standard population, was calculated. ESRD incidence and mortality were calculated, both in absolute terms and after correction for age, comorbidity and presence of renal tubulointerstitial fibrosis.

Results. The incidence rose from 33.3 patients per million (ppm)/year in 1985–94 to 46.5 ppm in 2005–14. The increase could in part be related to changes in renal biopsy policy. Large increases in Anti-neutropil cytoplasmic antibody (ANCA) vasculitis (ANCAV) (3.1–7.7 ppm/year) and focal segmental glomerulosclerosis (FSGS) (1.5–5.7 ppm/year) incidence were noted. The biopsy-proven prevalence of GN in 2014 was 748 ppm of which 155 ppm were being treated with dialysis or transplantation. Adjusted ESRD incidence fell by 25% during the study period, mortality by 62% and combined ESRD/mortality by 46%. The fall in ESRD incidence was limited to minimal change GN, FSGS, membranous GN and lupus nephritis, while reductions in mortality, and the combination of ESRD and/or death, were seen for nearly all GN diagnoses.

Conclusions. This study suggests that the incidence of GN has generally increased between 1985 and 2014, but some of the increase may be related to changes in renal biopsy policy. Major increases in FSGS and ANCAV incidence have occurred. The prognosis of GN, both as regards ESRD and mortality, has improved.

Keywords: ANCA, epidemiology, FSGS, glomerulonephritis, IgA nephropathy, lupus nephritis, membranous nephropathy, membranoproliferative glomerulonephritis, minimal change disease, prognosis

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INTRODUCTION

While there are many studies concerning the incidence and prevalence of glomerulonephritis (GN), fewer studies have been published concerning changes in incidence over time [1–15]. Most of these studies only cover the period before 2000 [1–4, 6, 9, 10, 13, 14], while others only have a short period of observation [5, 8, 11]. Many of the studies do not have a defined background population, and thus express relative frequencies rather than absolute incidence. Two large reviews of the studies have been published [12, 16]. The studies are characterized by considerable regional heterogeneity, but in general document a falling frequency of mesangioproliferative GN (MesPGN) and membranous GN (MGN), and an increase in focal segmental glomerulosclerosis (FSGS). The frequency of IgA nephropathy seems to have fallen in recent years.

Only three studies have presented long-term studies with recent data [12, 15, 17]. The existence of a national, comprehensive renal biopsy registry in Denmark since 1985 permits an evaluation of changes in absolute GN incidence over a long period of time. Furthermore, by linking these data with national registries of end-stage renal disease (ESRD), comorbidity and death, estimates of GN prognosis can be performed.

MATERIALS AND METHODS

All patients with GN, as confirmed by renal biopsy, and residing in Denmark between the years 1985 and 2014 inclusive, were included. The study was an observational study in epidemiology and followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting observational studies [18].

Renal biopsies

The renal biopsy information was derived from two registries:

1. Danish Renal Biopsy Registry (DANYRBI). This registry recorded all biopsies performed in Denmark between 1985 and 1999 [19]. The reproducibility of the glomerular diagnosis has been investigated and found acceptable with a kappa value of 0.61 [20].
2. Since 2000 renal biopsy results have been registered by the National Pathology Data Bank (Patobank).

The following Systematized Nomenclature of Medicine (SNOMED) diagnoses were included (SNOMED codes in parentheses): minimal changes disease (MCGN), (M00100, combined with proteinuria or nephrosis: S65080, S67020, or S67550), endocapillary GN (EndGN, M46870), FSGS (M53341), MesPGN (M46811, M46862), MGN (M68130), membranoproliferative GN (MPGN) (M46842), proliferative GN (ProlGN, M46810), Focal GN (M46861), extracapillary (crescentic) GN (M46880), anti-glomerular basement GN (AntiGBM) (S67400), ANCA vasculitis (ANCAV) (S76950), lupus nephritis (LN) (S38720). Due to inaccurate diagnosis of IgA nephropathy in early years, this diagnosis was combined with MesPGN, and classified as MesPGN. For most of these biopsies, the correct diagnosis will probably have been IgA GN and not primarily MesPGN. Most cases of EndGN will have been infection-related GN. For each patient, only one biopsy was included, being the first biopsy with a GN diagnosis. Patients <15 years old were excluded. For biopsies with multiple GN diagnoses, the first mentioned diagnosis was chosen, with the following exceptions: AntiGBM, ANCAV and LN were given first priority; MCGN was ignored in the presence of a more specific diagnosis. Microscopic diagnoses were supplemented with the following clinical diagnoses [International Classification of Diseases (ICD)] (*vide infra*) if these were compatible with microscopy: lupus (ICD-8 734.19, ICD-10 32.1–32.9), ANCAV (ICD-8 446.29, ICD-10 31.3), antiGBM (ICD-8 446.19, ICD-10 M31.0). The presence in the biopsy of tubulointerstitial fibrosis (M49000-M49005) was noted, but the registries do not contain information concerning degree of fibrosis.

The abbreviations used in this article are shown in Table 1.

Patient data

Patient sex and birthday were calculated from the national identity number. Dates of emigration and death were extracted from the National Patient Registry (LPR). The presence of the following clinical comorbidities at biopsy was also extracted: diabetes mellitus (DM), chronic heart disease, previous myocardial infarction, heart failure, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, chronic hepatic disease, cancer (excluding basocellular). Chronically reduced renal function was registered (SNOMED S65050, S65150, S65110, ICD-8 582.09, ICD-10 N03.x, N18.0, N18.3-18.9). ESRD was defined as requirement for maintenance dialysis or renal transplantation. Date of first dialysis or transplantation for these patients was extracted from the Danish Nephrology Registry. National population statistics by age were extracted from Statistics Denmark.

Statistics

Charlson comorbidity index (CCI) [21] was calculated from the registered comorbidity. Incidence rates were calculated for the whole population and by 10-year age group. Temporal changes were assessed using three cohorts: 1986–94, 1995–2004 and 2005–14. Age-standardized incidence rates were calculated from the European Standard population 2013 published by Eurostat, the Statistical Office of the European Union [22].

Table 1. Abbreviations

ANCA	Antineutrophil cytoplasmic antibody
ANCAV	ANCA vasculitis
AntiGBM	Anti-glomerular basement membrane glomerulonephritis
CCI	Charlson comorbidity index
DANYRBI	Danish Renal Biopsy Registry
DM	Diabetes mellitus
EndGN	Endocapillary glomerulonephritis
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
GN	Glomerulonephritis
ICD	International Classification of Diseases
LN	Lupus nephritis
LPR	National Patient Registry
LTF	Lost to follow-up
MCGN	Minimal change glomerulonephritis
MGN	Membranous glomerulonephritis
MesPGN	Mesangioproliferative glomerulonephritis
MemPGN	Membranoproliferative glomerulonephritis
ProlGN	Proliferative glomerulonephritis
SNOMED	Systematized Nomenclature of Medicine
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

Table 2. Distribution of patient number, relative per cent, age, sex and Charlson comorbidity index classified by renal diagnosis and cohort

	Number			Relative per cent			Age (years)			CCI		
Cohort	85-94	95-04	05-14	85-94	95-04	05-14	85-94	95-04	05-14	85-94	95-04	05-14
Minimal change	113	135	166	8.1	8.5	8.0	43.0 ±19	43.2 ±19	43.7 ±18	0.8	1.1[a]	1.5[c]
Endocapillary	49	31	24	3.5	2.0	1.2	42.6 ±1	52.2 ±20[a]	43.9 ±18	1.0	1.7[a]	2.0[b]
FSGS	62	83	255	4.5	5.3	12.3	45.3 ±16	46.7 ±16	50.7 ±17[a]	1.7	1.9	2.4[b]
Mesangioproliferative	480	490	487	34.6	31.0	23.5	43.5 ±17	45.8 ±18[a]	44.6 ±19	1.4	1.8[c]	2.2[c]
Membranous	189	216	257	13.6	13.7	12.4	50.0 ±17	54.0 ±16[a]	56.0 ±16[c]	1.3	1.7[b]	2.3[c]
Membranoproliferative	59	70	103	4.3	4.4	5.0	45.3 ±19	48.9 ±16	56.4 ±15[c]	1.5	2.1[b]	2.9[c]
Extracapillary	76	59	92	5.5	3.7	4.4	59.3 ±15	56.4 ±20	53.9 ±19[a]	2.1	2.1	2.5
AntiGBM	46	35	63	3.3	2.2	3.0	48.5 ±21	53.8 ±23	58.2 ±20[b]	2.1	2.8	2.9[b]
ANCAV	116	222	332	8.4	14.1	16.0	57.9 ±13	61.3 ±14	61.7 ±15[a]	1.8	2.5[c]	2.6[c]
Proliferative	19	23	35	1.4	1.5	1.7	55.8 ±18	46.9 ±21	44.1 ±19[a]	2.2	2.4	2.1
Focal	7	24	29	0.5	1.5	1.4	43.2 ±21	51.3 ±18	54.2 ±16	2.0	2.0	2.9
Lupus	172	191	233	12.4	12.1	11.2	38.5 ±17	37.0 ±15	41.1 ±16	1.5	1.8	1.9[b]
Total	1388	1579	2076	100	100	100	46.3 ±18	48.8 ±18[c]	50.6 ±18[c]	1.5	1.9[c]	2.3[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
$P < 0.001$ (versus 1985–94).
CCI shown as mean values, but analysed by Mann–Whitney.

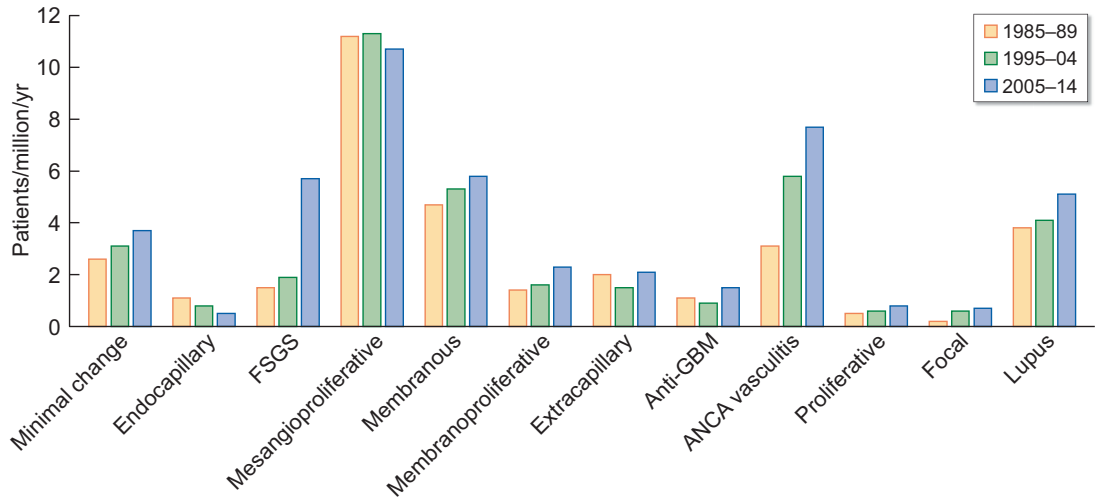

FIGURE 1: Adjusted incidence of renal diagnoses by cohort.

Normally distributed variables were compared using Student's *t*-test. Categorical and non-parametric variables were compared using Chi-square and Mann–Whitney.

Patients were followed until death, emigration or 1 January 2015. Patient survival [censored for lost to follow-up (LTF)], renal survival (time to ESRD, censored for patient death or LTF) and combined survival (time to death or ESRD, censored for LTF) were calculated using Kaplan–Meier analysis and Cox proportional hazards iterative regression analysis. Relative risks for the cohorts 1995–2004 and 2005–14, compared with 1985–94 as referent, were calculated after adjusting for patient age, sex, comorbidities and tubulointerstitial fibrosis. It was assumed that tubulointerstitial fibrosis was a marker of changes in biopsy indications, in that increased biopsy incidence of uraemic patients with reduced kidney size would increase the incidence of tubulointerstitial fibrosis. The Statistica (Tulsa, USA) program was used for the statistical analysis.

RESULTS

Patient details are shown in Table 2 and Figure 1. The mean age at biopsy rose from 46.3 ± 18 to 50.6 ± 18 years and CCI from 1.5 to 2.3 during the period of observation. The incidence of GN diagnoses is shown in Table 3. For most diagnoses, the absolute number and population-adjusted incidence of GN increased. However, the incidence of MesPGN, extracapillary GN and AntiGBM was unchanged, and EndGN incidence fell. Large increases in ANCAV [3.1–7.7 patients/million/year (ppm/year)] and FSGS (1.5–5.7 ppm/year) incidence were noted. The incidence of GN overall rose from 33.3 to 46.5 ppm/year. The biopsy-proven prevalence of GN in 2014 was 748 ppm of which 155 ppm were being treated with dialysis or transplantation. The relative frequency of the diagnoses for the period 2005–14 is compared with other published series in Table 4. Comparison between the studies is difficult due to differences in histological

Table 3. Relative frequency of diagnoses for the period 2005–14, compared with selected publications

Author	Present study[a]	Chiu et al. [23]	Polito et al. [24]	Hanko et al. [10]	Hou et al. [11]	Jegatheesan et al. [8]	Rychlik et al. [25]	Schena et al. [26]	Woo et al. [12]	Xu et al. [17]	Rivera et al. [27]	Wang et al. [15]
Land	Denmark	Taiwan	Brazil	UK	China	Australia	Czechoslovakia	Italy	Singapore	China	Spain	China
Publication date	2020	2018	2010	2009	2018	2016	2004	1997	2019	2016	2002	2019
Minimal change	8	19	12	11	12	5	10	6	20	5	12	12
Endocapillary	1	2	7		1	3	1	3		1		
FSGS	12	22	19	4	8	19	9	10	25		16	5
Mesangioproliferative/IgA[b]	24	29	19	43	51	30	31	40	31	56	20	39
Membranous	12	21	16		15	12	8	17	15	12	16	13
Membranoproliferative	5	3	3	10	1	3	4	5		2	9	
Extracapillary	4	5				12	3	4		1		
AntiGBM	3						1	0.3				
ANCAV	16		2				5	5			11	
Proliferative	2		4									
Focal	1									9		
Lupus	11		16		11	13	8	9		7	14	

[a]2005–14.
[b]Including Henoch–Schönlein.
Published figures adjusted for comparison. Figures in per cent.

classification, non-inclusion of secondary GN and subdivision of the results into cohorts and age groups. The published figures have therefore been adjusted to facilitate comparison.

The relationship of incidence to patient age is shown in Table 5 and Figure 2. The increase in incidence was particularly marked in age groups >50 years, but was also present in younger age groups.

In total, 692 (13.7%) biopsies contained tubulointerstitial fibrosis. This was evenly divided between diagnoses with some outliers: MCGN 16%, EndGN 5%, FSGS 28%. The proportion of biopsies with tubulointerstitial fibrosis rose during the period of observation (1985–94 5%; 1995–2004 14%; 2005–14 20%). The prevalence of chronically reduced renal function at biopsy increased (1985–94 47%; 1995–2004 57%; 2005–14 65%). The standardized incidence rate for biopsies without tubulointerstitial fibrosis also increased (1985–94 31.9 ppm/year; 1995–2004 32.0; 2005–14 37.3). This increase was common for most diagnoses, except for MesPGN, where incidence fell from 10.7 ppm/year to 8.0.

The changes in 1-, 5- and 10-year absolute incidence of ESRD, death and ESRD/death combined are shown in Table 6. An unadjusted bivariate Kaplan–Meier analysis, including the two cohorts 1995–2004 and 2005–14 was performed. With one (stated) exception, the significance values shown refer to the overall significance of the analyses. The number of patients with EndGN, ProlGN and Focal GN was too small for statistical analysis. The incidence of ESRD showed a heterogeneous pattern. For some diagnoses incidence rose in the period 1995–2004, and then fell. Only MCGN, ANCAV and LN showed a consistent fall in ESRD incidence. There was no overall change in absolute ESRD incidence.

For all diagnoses except MGN, mortality fell, and this was significant for MCGN, extracapillary GN, ANCAV and LN. MGN showed a heterogeneous pattern, with an initial rise followed by a significant fall. The overall 5-year mortality fell from 24% to 14%. Except for MesPGN, falls in combined ESRD and death were also seen and were significant for MCGN, extracapillary GN, ANCAV and LN. The combined 5-year ESRD/mortality fell from 36% to 26%.

Multivariate Cox proportional hazards analysis including age, sex and comorbidity was performed to investigate whether changes were independent of changes in patient age and comorbidity. The results are shown in Table 7. The number of patients with EndGN,AntiGBM, ProlGN and Focal GN was generally too small for statistical analysis. The adjusted ESRD incidence fell by 25% during the period. This reduction was considerable for the period 2005–14, where incidence fell 20% compared with 1995–2004. The fall was particularly notable for MCGN, FSGS, MGN and LN, but was only significant for the latter two diagnoses. No change in MesPGN ESRD incidence was seen. For nearly all diagnoses, significant falls in adjusted mortality were noted. The mortality fell by 38% in 1995–2004 compared with 1985–94, and by a further 39% after 2004. The total mortality fell by 62%. No fall in ProlGN mortality was seen, and the reductions for EndGN, MemPGN and Focal GN were insignificant. The incidence of ESRD or death in combination also fell by 46%: 24% in the first period of observation, and a further 29% in the second. The reduction was common for most major diagnoses. No reduction in the combination incidence was seen for EndGN, MemPGN, AntiGBM, ProlGN or Focal GN.

DISCUSSION

Cross-sectional results from the DANYRBI have previously been published [28]. Detailed reviews of previously published

Table 4. Absolute and adjusted incidence of GN classified by renal diagnosis and cohort

	Incidence (ppm)			Adjusted incidence (ppm[#])		
Cohort	85-94	95-04	05-14	85-94	95-04	05-14
Minimal change	2.7	3.1	3.7[b]	2.6	3.1	3.7
Endocapillary	1.2	0.7[a]	0.5[b]	1.1	0.8	0.5[b]
FSGS	1.5	1.9	5.7[c]	1.5	1.9	5.7[c]
Mesangioproliferative	11.3	11.3	10.8	11.2	11.3	10.7
Membranous	4.4	5.0	5.7[a]	4.7	5.3	5.8[a]
Membranoproliferative	1.4	1.6	2.3[b]	1.4	1.6	2.3[b]
Extracapillary	1.8	1.4	2.0	2.0	1.5	2.1
AntiGBM	1.1	0.8	1.4	1.1	0.9	1.5
ANCAV	2.7	5.1[c]	7.4[c]	3.1	5.8[c]	7.7[c]
Proliferative	0.4	0.5	0.8[a]	0.5	0.6	0.8[a]
Focal	0.2	0.6[b]	0.6[b]	0.2	0.6[b]	0.7[c]
Lupus	4.1	4.4	5.2[b]	3.8	4.1	5.1[b]
Total	32.7	36.3	46.2	33.3	37.3	46.5

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$ (versus 1985–94).
[#]ppm: patients per million inhabitants/year. Adjusted for European standard population 2013.

Table 5. Absolute incidence of GN classified by patient age and cohort

	Absolute incidence (ppm)		
	Cohort		
Age (years)	85-94	95-04	05-14
15–19	26.1	35.0	36.3[a]
20–29	30.9	31.4	37.4
30–39	29.0	27.3	39.1[c]
40–49	28.4	28.2	39.6[c]
50–59	42.0	45.1	46.9
60–69	48.7	55.9	66.0[c]
70–79	37.5	51.4[b]	70.0[c]
>79	7.0	17.4[b]	30.4[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$ (versus 1985–94).

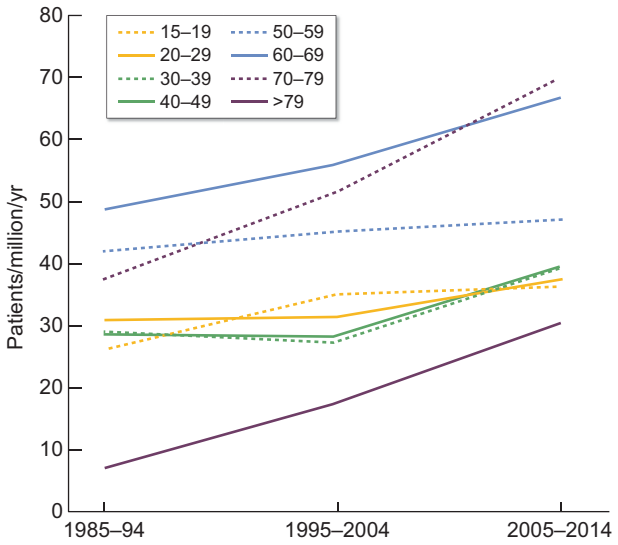

FIGURE 2: Absolute incidence of glomerulonephritis by age.

incidence studies are available [12, 16]. Comparison between the studies is difficult due to differences in histological classification, non-inclusion of secondary GN, and subdivision of the results into cohorts and/or age groups. A comparison of our latest results with selected publications is shown in Table 3. The published figures have been adjusted to facilitate comparison. The distribution in the present study is generally not atypical. IgA nephropathy is the most common diagnosis. MCGN, FSGS, MGN and LN are common diagnoses. EndGN, MPGN and crescentic GN are rare, while AntiGBM GN is excessively rare. The main difference is the high rate of ANCAV in recent years compared with most other countries (*vide infra*).

The primary aim of this study was to assess changes in the incidence and prognosis over time. This study has several advantages. The possibility of linking renal biopsy diagnoses to patient comorbidity, consequent death and/or ESRD, and general population statistics is unique. All registries involved are comprehensive. However, there are considerable methodological problems associated with assessing changes over so long a period.

The incidence of GN generally increased during the study period, except for EndGN, which fell. However, it would appear that the indications for renal biopsy were also increased. The average age of patients increased, and the increase in incidence was particularly marked among elderly patients. This is not the whole explanation, in that the incidence also increased among younger age groups (Table 5, Figure 2). Another possibility is that the indication for biopsy was increased to include patients with some degree of reduced renal size. Assuming that shrunken kidneys will have an increased degree of

Table 6. The 1-, 5- and 10-year incidence of end-stage renal disease (ESRD), death and the combination, classified by renal diagnosis and cohort

	1 år			5 år			10 år			Significance
ESRD	85-94	95-04	05-14	85-94	95-04	05-14	85-94	95-04	05-14	
Minimal change	0	2	0	3	2	2	12	3	0	P = 0.05
Endocapillary	0	16	18	2	16	18	2	16	18	
FSGS	5	7	2	24	21	16	40	38	33	
Mesangioproliferative	6	8	8	18	17	20	26	26	34	
Membranous	2	6	2	10	16	3	19	21	19	P < 0.01
Membranoproliferative	16	14	18	34	22	26	50	42	42	
Extracapillary	28	43	20	44	55	37	48	57	45	
AntiGBM	43	69	51	63	69	61	72	73	64	
ANCAV	12	20	7	18	30	18	38	37	24	P < 0.01
Proliferative	22	27	15	29	43	19	43	54	46	
Focal	33	13	22	50	18	22	50	21	22	
Lupus	12	18	13	14	12	6	20	18	9	P < 0.05*
Total	7	12	9	18	20	16	27	27	25	P < 0.05
Death										
Minimal change	6	4	1	15	8	3	23	14	15	P < 0.05
Endocapillary	28	36	8	21	22	8	12	10	8	
FSGS	7	0	4	18	10	14	34	26	25	
Mesangioproliferative	7	6	4	18	16	10	28	28	23	
Membranous	6	12	5	18	24	12	29	33	29	P < 0.05
Membranoproliferative	10	7	12	23	18	26	35	32	35	
Extracapillary	42	27	9	63	39	20	75	54	20	P < 0.001
AntiGBM	35	18	14	48	35	33	54	47	46	
ANCAV	20	18	11	41	34	23	57	47	43	P < 0.01
Proliferative	21	13	6	37	22	14	52	39	14	
Focal	14	4	8	57	8	20	57	42	48	
Lupus	7	3	4	20	13	11	27	19	12	P < 0.05
Total	11	9	6	24	20	14	34	30	25	P < 0.001
Combined										
Minimal change	6	6	1	17	9	5	38	14	16	P < 0.01
Endocapillary	12	26	20	21	36	26	28	45	26	
FSGS	10	8	6	37	30	24	57	51	41	
Mesangioproliferative	12	12	11	30	26	26	42	40	44	
Membranous	8	15	6	26	32	13	39	42	35	P < 0.001
Membranoproliferative	24	19	28	47	36	44	67	59	61	
Extracapillary	61	56	37	79	69	48	86	73	52	P < 0.01
AntiGBM	63	76	61	81	80	71	85	82	74	
ANCAV	26	32	20	49	46	34	67	58	49	P < 0.01
Proliferative	37	35	21	47	52	29	63	65	52	
Focal	42	17	25	71	25	39	71	49	50	
Lupus	10	10	6	30	20	16	40	31	20	P < 0.01
Total	17	18	14	36	32	26	48	44	40	P < 0.001

*1995–2004 versus 2005–14 only.
Figures in per cent.

tubulointerstitial fibrosis, and *vice versa*, this will result in an increased incidence of tubulointerstitial fibrosis in the biopsies, which is what we found. However, the standardized incidence of fibrosis-free GN also increased, so this is not the entire explanation.

These considerations are not relevant for FSGS and ANCAV, where the increases were dramatic. The rising incidence of FSGS is well described in the literature [1–3, 5, 6], with some exceptions [8, 11, 15], and is often ascribed to increases in FSGS due to environmental and lifestyle changes, in particularly the general increase in obesity [4, 5]. The increasing ANCAV incidence has also been previously described [29–31]. The cause is unknown. The increase in MCGN has previously been described [3, 15, 17], although one study has shown a stable incidence [5]. Similarly, a rising MGN has generally been seen after 2000 [11, 12, 15, 17]. We were unable to confirm previous studies, which have observed a falling incidence of MPGN [9, 13, 14, 17] and LN [11, 17]. Studies of IgA nephropathy incidence are heterogeneous, some finding an increase over time [5, 6, 10, 17], others an unchanged or falling incidence [9, 12, 15]. We found an unchanged incidence; interpretational difficulties are discussed below.

The overall absolute incidence of ESRD did not change during the study period. The incidence of ESRD generally rose from 1985–94 to 1995–2004, and then fell. The indication for dialysis and/or transplantation therapy has been widened to include elderly patients and those with Type 2 DM. Thus, the national incidence of ESRD rose from 62 to 139 ppm/year between 1990 and 2000 [32] after which it stabilized. This may explain the observed pattern. After adjusting incidence for age and

Table 7. Risk of ESRD, death and the combination, relative to the cohort 1985–94

	ESRD		Death		Combination	
	95-04	05-14	95-04	05-14	95-04	05-14
Minimal change	0.44 (0.17–1.13)	0.21 (0.04–1.02)	0.53 (0.30–0.93)[a]	0.29 (0.13–0.66)[b]	0.54 (0.32–0.90)[a]	0.31 (0.15–0.63)[b]
Endocapillary	2.52 (0.51–12.5)	2.56 (0.42–15.6)	0.51 (0.17–1.50)	0.37 (0.08–1.78)	1.15 (0.47–2.82)	0.99 (0.34–2.90)
FSGS	0.87 (0.51–1.49)	0.59 (0.34–1.01)[p=0.055]	0.49 (0.28–0.87)[a]	0.35 (0.19–0.65)[c]	0.75 (0.48–1.15)	0.48 (0.31–0.74)[b]
Mesangioproliferative	0.83 (0.65–1.06)	1.00 (0.74–1.34)	0.69 (0.55–0.86)[b]	0.44 (0.31–0.61)[c]	0.77 (0.64–0.92)[b]	0.76 (0.60–0.97)[a]
Membranous	1.01 (0.64–1.62)	0.32 (0.15–0.68)[b]	0.79 (0.58–1.08)	0.31 (0.19–0.49)[c]	0.88 (0.66–1.17)	0.32 (0.21–0.48)[c]
Membranoproliferative	0.73 (0.43–1.22)	0.76 (0.43–1.35)	0.75 (0.43–1.31)	0.56 (0.30–1.05)	0.83 (0.55–1.27)	0.78 (0.49–1.23)
Extracapillary	1.20 (0.68–2.12)	0.58 (0.31–1.08)	0.52 (0.34–0.81)[b]	0.20 (0.10–0.39)[c]	0.79 (0.53–1.19)	0.36 (0.22–0.59)[c]
AntiGBM	1.64 (0.89–3.05)	1.39 (0.79–2.44)	0.33 (0.17–0.66)[b]	0.26 (0.13–0.51)[c]	1.09 (0.64–1.87)	0.86 (0.53–1.39)
ANCAV	1.11 (0.73–1.71)	0.69 (0.43–1.09)	0.57 (0.42–0.76)[c]	0.37 (0.26–0.51)[c]	0.72 (0.55–0.95)[a]	0.45 (0.33–0.60)[c]
Proliferative	1.57 (0.52–4.80)	1.01 (0.28–3.68)	0.42 (0.14–1.31)	0.98 (0.17–5.75)	1.21 (0.52–2.85)	0.87 (0.32–2.38)
Focal	1.65 (0.18–14.9)	1.06 (0.10–11.4)	0.20 (0.04–0.93)[a]	0.38 (0.07–2.18)	0.74 (0.18–2.95)	0.67 (0.15–3.06)
Lupus	1.04 (0.65–1.65)	0.50 (0.26–0.96)[a]	0.59 (0.40–0.88)[b]	0.36 (0.21–0.61)[c]	0.76 (0.55–1.05)	0.43 (0.28–0.65)[c]
Total	0.94 (0.82–1.08)	0.75 (0.63–0.88)[c]	0.62 (0.55–0.69)[c]	0.38 (0.33–0.69)[c]	0.76 (0.69–0.85)[c]	0.54 (0.48–0.61)[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Adjusted for age, sex and comorbidity.

comorbidity, the incidence of ESRD fell by 25%. This fall was significant for MGN, and LN, and borderline significant for MCGN and FSGS.

No change in ESRD incidence was seen for ProlGN, Focal GN, EndGN, AntiGBM and MesPGN. While the first four diagnoses were too rare to permit reliable statistical analysis, the observation is probably true for MesPGN. The estimates of incidence and prognosis of MesPGN are problematic. No reliable estimates of the proportion of IgA nephritis in this study could be made. Younger patients with monosymptomatic haematuria and a normal renal function will rarely be biopsied, since the presumptive diagnosis is IgA nephropathy, and treatment nonspecific. Renal biopsy is reserved for patients with progressive renal failure or a high degree of proteinuria. This probably explains the poor prognosis of MesPGN in this study compared with other series [33, 34]. The incidence of non-fibrotic MesPGN fell from 10.7 to 8.0 ppm/year; the findings are not incompatible with a falling MesPGN incidence, as found by Woo *et al.* in a meta-analysis [12].

A reduction in the incidence of ESRD in recent years has been observed in Denmark for a number of renal diagnoses other than GN [35], and also a number of other countries [36]. This can possibly be ascribed to an increase in the use of antihypertensive therapy, especially renin–angiotensin system (RAS) blockers. These therapies will also have been used extensively for GN. Many forms of GN can now be treated with immunosuppressive therapy. However, effective immunosuppressive treatments for LN, MCGN, ANCAV, AntiGBM and MGN were already available at the start of the study period [37–44]. No data are available concerning possible increases in the use of immunosuppressive therapy in Denmark.

A general reduction in mortality and in combined mortality or ESRD was seen, both in absolute terms and after adjusting for age and comorbidity. The increased dialysis/transplantation indication could explain the reduced mortality, but not the combination. Any treatment that reduces uraemia progression (*vide supra*) can also be expected to reduce both ESRD incidence and mortality. It is also possible that this improvement is independent of renal disease, and just an expression of the increased longevity of the general population. Cardiovascular morbidity and mortality in the general population have fallen considerably, secondary to smoking cessation, antihypertensive therapy, RAS blockade, statin treatment, and improved therapies for acute coronary injury and heart failure. This may be particularly relevant for renal patients, who have a massively increased risk of cardiovascular disease [45].

Several criticisms of this study can be made. As previously mentioned, changes in biopsy indication and indications for dialysis therapy imply that the reality of observed changes over time can be questioned. Due to previous registration problems, the incidence of IgA nephropathy could not be included. The limited indications for renal biopsy in patients with MesPGN suggest that the results of this group will be unreliable. Data after 2014 were unavailable.

With these caveats, this study suggests that the incidence of GN has generally increased between 1985 and 2014, but some of the increase may be related to changes in renal biopsy policy. Major increases in FSGS and ANCAV have occurred. The prognosis of GN, both as regards ESRD and mortality, has improved despite an increased burden of comorbidity.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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